In vivo molecular MRI of cell survival and teratoma formation following embryonic stem cell transplantation into the injured murine myocardium.

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Public Summary:
Our work reports the first MRI reporter gene in human and mouse embryonic stem cells (ESC) to demonstrate in vivo molecular MRI signal of cell survival following transplantation into the murine model of myocardial injury. The human and mouse ESC have been bioengineered using a lentiviral vector to express two cell surface antigens and firefly luciferase as molecular markers of cell viability. Intravenous administration of superparamagnetic iron oxide nanoparticle-conjugated antibody against these antigens has generated significant in vivo MRI signal of cell survival. This molecular MRI signal is validated by the bioluminescence signal from the firefly luciferase enabling multi-modality confirmation of human and mouse ESC survival. The originality of this work is two-fold. First, a robust technique to amplify molecular MRI signal specific to post-transplantation survival of ESC has been developed. MRI combines chemical sensitivity of nuclear magnetic resonance with high spatial and temporal resolution. It routinely offers sub-millimeter resolution with temporal resolution in the millisecond range and intrinsically superior contrast mechanism. However, MRI suffers from poor sensitivity. The methodology reported in our work overcomes this problem and detects molecular survival signal of transplanted cells. In cell therapy, the transplanted cells at the very least must survive to restore the injured end-organ. This fundamental biological process must be readily monitored in vivo before cell therapy becomes a clinical reality. Second, MRI has become the predominant imaging modality to assess the precise effects of cell therapy on the recipient organ. Our technology extends this capability by detecting abnormal survival or pluripotent proliferation of the transplanted cells in vivo. Teratoma formation can be detected at very early stage and accurate assessment of their effects on the surrounding tissue is possible. The immediate application of this technology is in the detection of early teratoma formation. This capability addresses one of the critical bottlenecks in clinical translation of human ESC and induced pluripotent stem cells. Second, the potential application of this research comes from the flexibility and the ease of manipulating this molecular platform to detect any engraftment parameters in vivo.

Scientific Abstract:
Embryonic stem cells (ESCs) have shown the potential to restore cardiac function after myocardial injury. Superparamagnetic iron oxide nanoparticles (SPIO) have been widely employed to label ESCs for cellular MRI. However, nonspecific intracellular accumulation of SPIO limits long-term in vivo assessment of the transplanted cells. To overcome this limitation, a novel reporter gene (RG) has been developed to express antigens on the ESC surface. By employing SPIO-conjugated monoclonal antibody against these antigens (SPIO-MAb), the viability of transplanted ESCs can be detected in vivo. This study aims to develop a new molecular MRI method to assess in vivo ESC viability, proliferation, and teratoma formation. The RG is designed to express 2 antigens (hemagglutinin A and myc) and luciferase on the ESC surface. The two antigens serve as the molecular targets for SPIO-MAb. The human and mouse ESCs were transduced with the RG (ESC-RGs) and transplanted into the peri-infarct area using the murine myocardial injury model. In vivo MRI was performed following serial intravenous administration of SPIO-MAb. Significant hypointense signal was generated from the viable and proliferating ESCs and subsequent teratoma. This novel molecular MRI technique enabled in vivo detection of early ESC-derived teratoma formation in the injured murine myocardium. Magn Reson Med, 2011. (c) 2011 Wiley-Liss, Inc.

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